PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials
AUTHORS	Jeddi, Haron; Busse, Jason; Sadeghirad, Behnam; Mitchell, Levine; Zoratti, Michael; Wang, Li; Noori, Atefeh; Couban, Rachel; Tarride, Jean-Eric

VERSION 1 – REVIEW

REVIEWER	Joshua Aviram University of Haifa Faculty of Social Welfare and Health Sciences
REVIEW RETURNED	11-Nov-2022

GENERAL COMMENTS	Medical cannabis versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials The study is a review and meta-analysis paper of RCTs that aims to compare the benefits and risks of medical cannabis vs. opioids for chronic pain patient population, but only studies with a moderate duration or longer qualified for the analysis. This is a very important paper that the clinical and academic fields could benefit from when published. Nonetheless, I have few major concerns, cannabis based medications are not medical cannabis by term and it makes the entire results hard to differentiate in real world settings for a physician that does not know all the literature and the introduction needs to include an explanation on the complexity of cannabis compared to the simplicity of a single synthetic molecule for opioids. I will describe my specific inputs based on the authors titles: Abstract: I am missing vital comparisons to answer this study question, regarding comparisons of adverse events by body systems, there is extensive data on that (Aviram, J., & Samuelly-Leichtag, G. (2017). Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain physician, 20(6), E755.) which must contribute to the safety comparisons. There is probably a problem with the definition of "medical cannabis" in the entire study. From my experience, most RCTs regarding cannabis and pain assessed cannabis based medications (CBMs; such as Nabiximoles, Nabilone, Dronabinol) and not medical cannabis (i.e., full spectrum cannabis flowers by inhalation or by oral extract ingestion). Thus, following specifying of the products used, this term should be explained and changed accordingly. this should be stated in the limitations as in real world setting patients are more likely to consume medical cannabis flowers. Opioids used also needs to be clarified in the text and not just in the

	appendix, as in most directly comparisons, the opioids used like Codeine, are not those used in real world settings, which are using Percocet, Targin, Fentanyl patches etc. Due to the above, the conclusions needs to be more cautious and explain the impact of real world clinical decisions. What is already known section Consider relating to the EFIC guidelines as well. What this study ads Fix the typo to "adds" There is a false presentation that all 90 studies compared opioids to cannabinoids directly, as there is no list for the papers included it is not visible, but as the authors mentioned, some of the comparisons for each treatment was made to placebo and not to each other. Thus, there is a need to breakdown this number here to- direct comparison, and to 2 additional numbers for placebo comparisons. Introduction: Page 6, line 35- EFIC recommendations are quite different, approving for inhaled but not smoked products. The authors should cite that numerous previous reviews and meta-analyses were published on chronic pain and relate to their results. The authors should cite the real-world evidence from the international registries that were published on cannabis that showed superior results comparing to RCTs settings. The authors should explain the complexity of the cannabis plant with >400 components that we are not sure which of them is the active or which combination or route of administration and that most RCTs were conducted only with THC, CBD or only THC/CBD and not the full plant. Methods: Consider including grey literature from clinicaltrials.gov to check for unpublished results. Consider to add comparison of results to studies with 4-12 weeks duration and >12 weeks separately. Instead of excluding combination drugs opioids, consider a sub-analysis for these as it is important for real world applications and decisions. Page 8 line 5- state who from the authors took which role in this. Data analysis: please state if in all studies, the tools used were validated. Page 9 line 13: consider adding a comparison for clinically important difference (CID) of >30% and >50% pain reduction from baseline. Results: Page 12 lines 10-15- add references to all mentioned studies. Page 12 line 22- specify the diagnoses of neuropathic pain (NP) and those of non-NP and mixed and specify the distribution of the studies on these. Consider adding a comparison between them for efficacy and harms. Table 1- according to this table, it is clear that the title of the study must be revised as most studies were not a direct comparison between cannabis and opioids. there is a typo on CBDC. please specify the cannabis products and not THC/CBD (probably Nabiximoles)- same for appendixes. Discussion: page 18 line 32: revise to make it clear that the comparison is indirect. Page 18 line 55: add the risk of opioid induced hyperalgesia in long

	term opioids use (Portenoy, R. K., Farrar, J. T., Backonja, M. M., Cleeland, C. S., Yang, K., Friedman, M., ... & Richards, P. (2007). Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. The Clinical journal of pain, 23(4), 287-299.). Page 20 line 17- please add references to the statement that cannabis may cause overdose as opioids.

REVIEWER	Thammanard Charernboon Thammasat University
REVIEW RETURNED	08-Dec-2022

GENERAL COMMENTS	The manuscript is interesting, comprehensive, and well written. I have a few suggestions: 1. Abstract: The abstract's conclusion may be a little too strong. It should be noted that the findings were mostly based on a low level of evidence with only 0-1 direct evidence. 2. Data analysis: How the authors converted continuous measures to some scales (e.g., VAS, SF-36, etc.). Why did you choose this method over z-scores or other comparable techniques? 3. It would be interesting to add one more subgroup analysis: CBD vs. THC vs. mixed CBD/THC (or others). 4. Please add more comments about transitivity and publication bias to the discussion.

REVIEWER	C Feng University of Rochester, Department of Biostatistics
REVIEW RETURNED	11-May-2023

GENERAL COMMENTS	The authors did a very comprehensive meta analysis to compare the benefits and harms of opioids and medical cannabis for chronic non-cancer pain. The selection of published clinical trials and statistical analysis support the conclusion. My only concern is that the paper may be too long for a single issue of the journal.

REVIEWER	D Moore Rutgers University, Biostatistics
REVIEW RETURNED	16-May-2023

GENERAL COMMENTS	This is a large and thorough meta-analysis of cannabis versus opioids for chronic noncancer pain. The search process for studies to include was thorough and appropriate. The findings will be of great value to clinicians dealing with chronic pain. I have two concerns, mainly about the statistical methods: 1. Network meta-analysis is an important tool, and the authors refer to the Hutton et al. PRISMA extension statement for network meta-analyses. Still, it would help readers to expand on the value of network analysis for this study, possibly including a graph of the network to summarize the numbers of studies and different treatments, such as Figure 1 in the Hutton et al. reference. 2. The authors include several funnel plots in the appendix which to this reader appear to show some publication bias. Please comment on these funnel plots and explain how this may or may not affect their conclusions.

REVIEWER	Isabel Allen UCSF, Biostatistics & Epidemiology
REVIEW RETURNED	24-May-2023

GENERAL COMMENTS	Very comprehensive and well done systematic review and meta-analysis. It would be great to see a network plot with strength of evidence in the main paper since the tables are sometimes difficult to decipher.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Joshua Aviram, University of Haifa Faculty of Social Welfare and Health Sciences

General Comments to the Author:

Medical cannabis versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials
The study is a review and meta-analysis paper of RCTs that aims to compare the benefits and risks of medical cannabis vs. opioids for chronic pain patient population, but only studies with a moderate duration or longer qualified for the analysis. This is a very important paper that the clinical and academic fields could benefit from when published.

Comment #1: Nonetheless, I have few major concerns, cannabis based medications are not medical cannabis by term and it makes the entire results hard to differentiate in real world settings for a physician that does not know all the literature and the introduction needs to include an explanation on the complexity of cannabis compared to the simplicity of a single synthetic molecule for opioids.

Answer to Comment #1: We appreciate the reviewer's comments on the differences between cannabis-based medicines and medical cannabis. In our case, we included all types of cannabis (herbal, synthetic, semisynthetic, and plant derived) for therapeutic use, as mentioned in the "data sources and searches" section of the methods and aligned with our study protocol (reference 16 in our manuscript[1]),

To provide clarity, we modified our title by replacing "medical cannabis" with "cannabis for medical use" as shown below (underlined text represent new text while deletions are represented by ~~strikethrough~~).

- *"~~Medical cannabis~~ Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials."*

[1] Jeddi M, Levine M, Busse JW, Sadeghirad B, *et al*. A systematic review and network meta-analysis of cannabis versus opioids for the treatment of chronic non cancer pain. PROSPERO 2020 CRD42020185184.)

We updated the abstract to make it clear that all types of cannabis, including cannabis-based medicines were included in our study as shown below (additions are represented by underlined text and deletions by ~~strikethrough~~).

- "*Randomized trials comparing ~~medical~~ any type of cannabis for medical use or opioids, against each other or placebo, with patient follow-up ≥4 weeks."*

We also added the following sentences in the new "Strengths and limitations of this study" section after the abstract (as requested by the Editor, see answer to Editor comment #3) to clarify that inhaled cannabis studies were not eligible for our review and that our results may not be generalizable to products commonly used in a real-world setting as shown below by the underlined text.

- *Twenty-four RCTs evaluating cannabis for medical use were included in our review; however, none of these trials administered inhaled forms of cannabis and the generalizability of our findings to smoked or vaporized cannabis is uncertain.*

Abstract:

Comment #2: I am missing vital comparisons to answer this study question, regarding comparisons of adverse events by body systems, there is extensive data on that (Aviram, J., & Samuelly-Leichtag, G. (2017). Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. Pain physician, 20(6), E755.) which must contribute to the safety comparisons.

Answer to Comment #2: Thank you for sharing this reference. Although we could not add this point in the abstract due to constraints in the word count limit, we have updated our Discussion section to include findings from Aviram, J., & Samuelly-Leichtag, G. (2017) and Wang (2021) on adverse events versus placebo.

The following underlined text has been added in the Discussion section.

- *"*Further*, a network meta-analysis found no evidence to support important differences in pain relief, functional improvement, or gastrointestinal adverse events between different types of opioids.[148] In order to facilitate pooling, we reported harms as discontinuations due to adverse events instead of reporting specific adverse events experienced by trial participants. In other meta-analyses of RCTs, cannabis for medical use was associated with greater central nervous system and gastrointestinal adverse events, versus placebo.[149,150] Both opioids and cannabis can result in use disorders and overdose…:"*

Comment #3: There is probably a problem with the definition of "medical cannabis" in the entire study. From my experience, most RCTs regarding cannabis and pain assessed cannabis based medications (CBMs; such as Nabiximoles, Nabilone, Dronabinol) and not medical cannabis (i.e., full spectrum cannabis flowers by inhalation or by oral extract ingestion). Thus, following specifying of the products used, this term should be explained and changed accordingly. this should be stated in the limitations as in real world setting patients are more likely to consume medical cannabis flowers.

Answer to comment #3: Several changes were made to address this comment as explained below:

(1) We updated the abstract to make it clear that all types of cannabis, including CBMs were included in our study as shown below (additions are represented by underlined text and deletions by ~~strikethrough~~).

- "*Randomized trials comparing ~~medical~~ any type of cannabis for medical use or opioids, against each other or placebo, with patient follow-up ≥4 weeks."*

(2) We updated our title to "cannabis for medical use" to include cannabis-based medicines and other forms of cannabis that were considered in our search strategy as per our **Answer to Comment #1**.

(3) The 3rd bullet point of the new 'Strengths and limitations of this study' section located after the abstract further clarifies this point as shown below.

- *Twenty-four RCTs evaluating cannabis for medical use were included in our review; however, none of these trials administered inhaled forms of cannabis and the generalizability of our findings to smoked or vaporized cannabis is uncertain.*

Comment #4: Opioids used also needs to be clarified in the text and not just in the appendix, as in most directly comparisons, the opioids used like Codeine, are not those used in real world settings, which are using Percocet, Targin, Fentanyl patches etc. Due to the above, the conclusions needs to be more cautious and explain the impact of real world clinical decisions.

Answer to comment #4: Thank you for pointing out this issue. However, as already mentioned in our manuscript, previous studies have not shown differences between different opioids (see references number 148)

Comment #5: What is already known section
Consider relating to the EFIC guidelines as well.

Answer to comment #5. We have deleted this section based on the Editor's comments (comment #2 from the Editor).

Comment #6: What this study ads
Fix the typo to "adds"
There is a false presentation that all 90 studies compared opioids to cannabinoids directly, as there is no list for the papers included it is not visible, but as the authors mentioned, some of the comparisons for each treatment was made to placebo and not to each other. Thus, there is a need to breakdown this number here to- direct comparison, and to 2 additional numbers for placebo comparisons.

Answer to comment #5. We have deleted this section following the Editor's suggestion (comment #2) and addressed the reviewer's comment in the new section 'Strengths and limitations of this study' after the abstract by including the following bullet point:

- *"For the comparison of cannabis for medical use and opioids, the majority of our outcomes were informed by indirect evidence since we found only one trial directly comparing both interventions for chronic pain."*

Introduction:

Comment #7: Page 6, line 35- EFIC recommendations are quite different, approving for inhaled but not smoked products.
The authors should cite that numerous previous reviews and meta-analyses were published on chronic pain and relate to their results.

Answer to comment #7: We added the EFIC recommendations on page 6 as suggested.

The following underlined text has been added and deletions are represented by ~~strikethrough~~

- *"Alternately, a 2021 BMJ Rapid Recommendation made a conditional recommendation to offer a trial of non-inhaled ~~medical~~ cannabis for medical use for people living with chronic pain if standard care was insufficient.[13] The European Pain Federation (EFIC) also issued a position paper stating that cannabis based medicines can be used by experienced physicians when guideline recommended 1st and 2nd line therapies for chronic pain do not provide sufficient benefit. The position paper also advised against smoking cannabis in favor of oil extracts or vaporizers for inhalation of dried cannabis.[14] We undertook a systematic review and network meta-analysis of randomized controlled trials (RCTs) to explore the comparative benefits and harms of ~~medical~~ cannabis and opioids for chronic noncancer pain."*

Comment #8: The authors should cite the real-world evidence from the international registries that were published on cannabis that showed superior results comparing to RCTs settings.

Answer to comment #8: Thank you for the suggestion. Real-world evidence (RWE) comes from multitude of sources including registries, healthcare and insurers records, but is based on observational data which is prone to confounding and other biases and may be associated with issues that can impact the determination of cause and effect. As such we think adding evidence of benefit or superiority from RWE in the introduction may not be appropriate.

Nonetheless, we modified the discussion section (additions are represented by underlined text and deletions by ~~strikethrough~~) to indicate that observational data have shown results *in favor of cannabis for medical use* and cited supporting references as follows:

- *"In part, because some observational studies (but not others[132,133]) have shown an association between legalization of cannabis for medical use and reduced prevalence of opioid use disorder and opioid overdose.[134,135] Although prone to measured and unmeasured confounding bias, recent observational studies and studies using registry data have also shown favourable improvements in pain and health related quality of life outcomes for cannabis for medical use when compared to opioids.[136-139(references 1-4 below).] Moreover, users of ~~medical~~ cannabis for medical use acknowledge substitution of prescription medication, particularly opioids, as a common motive.[140,141]*

References:

(1) Harris M, Erridge S, Ergisi M, Nimalan D, Kawka M, Salazar O, Ali R, Loupasaki K, Holvey C, Coomber R, Usmani A, Sajad M, Hoare J, Rucker JJ, Platt M, Sodergren MH. UK Medical Cannabis registry: an analysis of clinical outcomes of medicinal cannabis therapy for chronic pain conditions. Expert Rev Clin Pharmacol. 2022 Apr;15(4):473-485. doi: 10.1080/17512433.2022.2017771. Epub 2021 Dec 31. PMID: 34937477.

(2) Tait J, Erridge S, Holvey C, Coomber R, Usmani A, Sajad M, Hoare J, Khan S, Weatherall M, Rucker JJ, Platt M, Sodergren MH. Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry. Expert Rev Neurother. 2023 Apr;23(4):413-423. doi: 10.1080/14737175.2023.2195551. Epub 2023 Apr 6. PMID: 37021592.

(3) Meng H, Page MG, Ajrawat P, Deshpande A, Samman B, Dominicis M, Ladha KS, Fiorellino J, Huang A, Kotteeswaran Y, McClaren-Blades A, Kotra LP, Clarke H. Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients. Can J Anaesth. 2021 May;68(5):633-644. English. doi: 10.1007/s12630-020-01903-1. Epub 2021 Jan 20. PMID: 33469735.

(4) Vickery AW, Roth S, Ernenwein T, Kennedy J, Washer P. A large Australian longitudinal cohort registry demonstrates sustained safety and efficacy of oral medicinal cannabis for at least two years. PLoS One. 2022 Nov 18;17(11):e0272241. doi: 10.1371/journal.pone.0272241. PMID: 36399463; PMCID: PMC9674134.

Comment #9: The authors should explain the complexity of the cannabis plant with >400 components that we are not sure which of them is the active or which combination or route of administration and that most RCTs were conducted only with THC, CBD or only THC/CBD and not the full plant.

Answer to comment #9: Thank you for your suggestion. We added the following underlined text to the discussion.

- *As such, our results may not reflect outcomes where opioids or cannabis are used in combination with other drugs. The cannabis plant contains over 500 chemical substances and the main cannabinoids included in most RCTs are THC, CBD, or THC/CBD and not the full plant. We pooled different opioids and types of cannabis for medical use that may not be common forms of products used in the real-world; however, subgroup analysis suggests that effects for chronic pain are similar across different opioids and ~~medical~~ cannabis for medical use products[148,149]"*

The 3rd bullet point of the new 'Strengths and limitations of this study' section also highlights that our results may not be generalizable to products used in a real-world setting, as shown below.

- *Twenty-four RCTs evaluating cannabis for medical use were included in our review; however, none of these trials administered inhaled forms of cannabis and the generalizability of our findings to smoked or vaporized cannabis is uncertain.*

Methods

Comment #10: Consider including grey literature from clinicaltrials.gov to check for unpublished results.

Answer to comment #10: As indicated in our study protocol registered in PROSPERO (reference 15 of our paper) and in our Methods (see Data Sources and Searches),

we searched the Cochrane Library Central database which includes records from clinicaltrials.gov. Details are available at: https://www.cochranelibrary.com/central/central-creation.

We used information provided in clinicaltrials.gov to identify eligible trials and/or to complete missing data items not provided in trial publications. For example, we had 1 study where results

from clinicaltrials.gov were used (NCT00710424. A Study of Sativex® for Pain Relief Due to Diabetic Neuropathy: https://ClinicalTrials.gov/show/NCT00710424, 2006.)

For clarity we updated our discussion section with the following underlined text.

- *"Our study, which is the first network meta-analysis exploring the comparative effectiveness of ~~medical~~ cannabis for medica use and opioids for chronic noncancer pain, has several strengths. We conducted a comprehensive search strategy, including grey literature from clinicaltrials.gov, used the GRADE approach to appraise the certainty of evidence for treatment effects and followed GRADE guidance for communicate our findings."*

Comment #11: Consider to add comparison of results to studies with 4-12 weeks duration and >12 weeks separately.

Answer to comment #11: We decided not to perform separate analysis for 4-12 weeks follow-up duration and >12 weeks for the following reasons:

1) There were only 3 cannabis for medical use RCTs with >12 weeks duration, thus limiting the power of such an analysis.

2) As shown in eTable 7 and eTable 8 (Supplement files), we performed network meta-regressions with follow-up time across all outcomes and the results with the exception of discontinuations due to adverse events (for non-enriched trials) showed no associations between study duration and outcomes. Performing subgroup analyses on discontinuations due to adverse events (non-enriched trials) for studies >12 weeks versus 4-12 weeks would be again underpowered because only 3 RCTs would inform the >12 data.

3) As discussed in Altman and Royston (2006)[2] and Dawson and Weiss (2022)[3], subgroup analyses by dichotomizing a continuous variable when there is no indication of a change in effect is not recommended and may lead to loss of statistical power. Despite that we performed subgroup analyses for studies with median 4-8 weeks duration and > 8 weeks (Table 3 and eTable 6). In the absence of a clear cut-point, the median is a common approach.[2]

[2] Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006 May 6;332(7549):1080. doi: 10.1136/bmj.332.7549.1080. PMID: 16675816; PMCID: PMC1458573;

[3] Dawson, N. V., & Weiss, R. (2012). Dichotomizing continuous variables in statistical analysis: A practice to avoid [Editorial]. *Medical Decision Making*, *32*(2), 225–226. https://doi.org/10.1177/0272989X12437605

Comment #12: Instead of excluding combination drugs opioids, consider a sub-analysis for these as it is important for real world applications and decisions.

Answer to comment #12: We excluded trials with combination drugs because results may be confounded by the additional drugs. To address the reviewer's comment, we updated our limitations section of the discussion with the following additional underlined text:

- *None of the trials eligible for our review explored inhaled cannabis, and our results may not be generalizable to this method of administration. We excluded trials with combination drugs because results may be confounded by the additional drugs. As such, our results may not reflect outcomes where opioids or cannabis are used in combination with other drugs (e.g. tramadol and acetaminophen).*

Comment #13: Page 8 line 5- state who from the authors took which role in this.

Answer to comment #13: Thank you for the suggestion. We updated the section and included initials of authors who performed the role.

The following underlined text has been added:

- *For all eligible trials, we (W.L., N.A. C.R, J.H.M) collected information regarding study characteristics, intervention details, patient characteristics, and all patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.*

Comment #14: Data analysis: please state if in all studies, the tools used were validated.

Answer to comment 14: To address the reviewer's comment, we updated the data analysis section with the following additional underlined text:

- *"Instruments used in the RCTs mostly consisted of the visual analogue scale (VAS) and the numerical rating scale (NRS) for measuring pain intensity and sleep quality, and the Short Form-36 for other important patient outcomes (e.g. physical functioning, emotional functioning, role functioning, social functioning). These instruments have been shown to be reliable and valid in chronic pain populations[22-24 (references 1- 3below).] eTable 1 lists additional instruments that were used to capture patient-important outcomes, and references supporting their psychometric properties."*

References:

(1) Patel KV, Amtmann D, Jensen MP, Smith SM, Veasley C, Turk DC. Clinical outcome assessment in clinical trials of chronic pain treatments. Pain Rep. 2021 Jan 21;6(1):e784. doi: 10.1097/PR9.0000000000000784. PMID: 33521482; PMCID: PMC7837993.

(2) Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S; European Palliative Care Research Collaborative (EPCRC). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011 Jun;41(6):1073-93. doi: 10.1016/j.jpainsymman.2010.08.016. PMID: 21621130.

(3) Safikhani S, Gries KS, Trudeau JJ, Reasner D, Rüdell K, Coons SJ, Bush EN, Hanlon J, Abraham L, Vernon M. Response scale selection in adult pain measures: results from a literature review. J Patient Rep Outcomes. 2018 Sep 6;2:40. doi: 10.1186/s41687-018-0053-6. PMID: 30238085; PMCID: PMC6127068.

Comment #15: Page 9 line 13: consider adding a comparison for clinically important difference (CID) of >30% and >50% pain reduction from baseline.

Answer to comment #15: Twenty-two RCTs involving opioids evaluated 30% or 50% pain reductions from baseline while only four cannabis for medical use RCTs reported these outcomes. As such, an analysis exploring the comparative effectiveness of opioids vs. cannabis for medical use using a CID of 30% or 50% would be underpowered.

Based on the above, we did not make any changes in response to comment #15.

Results

Comment #16: Page 12 lines 10-15- add references to all mentioned studies.

Answer to comment #16: References of studies included in our review have been added.

Comment #17: Page 12 line 22- specify the diagnoses of neuropathic pain (NP) and those of non-NP and mixed and specify the distribution of the studies on these. Consider adding a comparison between them for efficacy and harms.

Answer to comment #17: Due to the many different pain conditions, we updated the sentence to specify that details on the pain condition in each trial can be found in eTable 1 in the Supplement –Baseline characteristics of eligible randomized controlled trials.

For clarity, the following underlined text has been added in the results section:

- *"Twenty-nine trials enrolled patients with neuropathic pain, 60 with non-neuropathic pain, and 1 trial enrolled patients with mixed pain. (Table 1, & eTable 2 in Supplement for details on the pain conditions and other baseline characteristics)."*

Subgroup analyses for neuropathic pain versus non-neuropathic pain across all outcomes were already reported in our original manuscript (Table 3 manuscript & eTable 6 in Supplement).

For clarity, the following underlined text has been added in the results section:

- *"We found no evidence of credible subgroup effects based on type of pain condition (neuropathic versus non-neuropathic), length of follow-up, sample size, or opioid dose (Table 3, eTable 6-10 in Supplement)."*

Comment #18: Table 1- according to this table, it is clear that the title of the study must be revised as most studies were not a direct comparison between cannabis and opioids.

Answer to comment #18: We appreciate the reviewer's comment. However as per the Cochrane definition for network-meta analysis (copied below), we feel our title is consistent with our methods as two key endpoints (pain and discontinuations due to adverse events, non-enriched studies) were informed by direct and indirect evidence, which satisfy the definition of a network meta-analysis as per Cochrane Handbook for Systematic Reviews of Interventions version 6.3.[4]

We also believe that the additional underlined text in the new 'Strengths and limitations of this study' section requested by the Editor addresses the reviewer's comment:

- *For the comparison of cannabis for medical use and opioids, the majority of our outcomes were informed by indirect evidence since we found only one trial directly comparing both interventions for chronic pain.*

Comment #19: Table 1 - there is a typo on CBDC.

[4] Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Chapter 11: Undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.)

Answer to comment #19: Thank you for catching this typo, which we have corrected.

Comment #20: please specify the cannabis products and not THC/CBD (probably Nabiximoles)- same for appendixes.

Answer to comment #20: Product names (e.g. Nabiximoles) were not always reported in the RCTs and therefore we cannot update table 1 in a consistent manner. However, we addressed the reviewer's comment by updating eTable 2 in the Supplement to include product names when reported in the RCTs.

Discussion:

Comment #21: page 18 line 32: revise to make it clear that the comparison is indirect.

Answer to comment #20: Please refer to our response above to comment #18

Comment #22: Page 18 line 55: add the risk of opioid induced hyperalgesia in long term opioids use (Portenoy, R. K., Farrar, J. T., Backonja, M. M., Cleeland, C. S., Yang, K., Friedman, M., ... & Richards, P. (2007). Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. The Clinical journal of pain, 23(4), 287-299.).

Answer to comment #22: The reference from the reviewer is from an observational study and our focus is on RCTs. To address to the review's comment, we updated the discussion with the following underlined text (deletions are represented by ~~Strikethrough)~~:

- *"Both opioids and cannabis for medical use can result in use disorders[151,152] while opioids can also result in fatal and non-fatal overdose; however, we were unable to construct a network to explore the comparative risk of these important harms ~~due to lack of reporting~~ as RCTs are poorly suited to detect rare harms or harms that take a while to manifest ~~among clinical trials~~."*

Comment #23: Page 20 line 17- please add references to the statement that cannabis may cause overdose as opioids.

Answer to comment #23: We modified that particular sentence with the following underlined text and provide a supporting reference for opioid and cannabis use disorder[5,6] (deletions are represented by ~~strikethrough~~):

- *"Both opioids and cannabis for medical use can result in use disorders[151,152] while opioids can also result in fatal and non-fatal overdose; however, we were unable to construct a network to explore the comparative risk of these important harms ~~due to lack of reporting~~ as RCTs are poorly suited to detect rare harms or harms that take a while to manifest ~~among clinical trials~~."*

Reviewer: 2 Dr. Thammanard Charernboon, Thammasat University

Comments to the author: The manuscript is interesting, comprehensive, and well written. I have a few suggestions:

Comment #1: Abstract: The abstract's conclusion may be a little too strong. It should be noted that the findings were mostly based on a low level of evidence with only 0-1 direct evidence.

Answer to comment #1: Our conclusion states that cannabis for medical use 'may' be similarly effective and less harmful. We followed the recommended language from GRADE on communicating findings of systematic reviews.[7]

The following bullet point provided in the new 'Strengths and limitations of this study' section located after the abstract (as requested by the Editor) addresses the reviewer's comment with respect to the number of direct studies informing our review:

- *"For the comparison of cannabis for medical use and opioids, the majority of our outcomes were informed by indirect evidence since we found only one trial directly comparing both interventions for chronic pain."*

[5] Connor JP, Stjepanović D, Le Foll B, Hoch E, Budney AJ, Hall WD. Cannabis use and cannabis use disorder. Nat Rev Dis Primers. 2021 Feb 25;7(1):16. doi: 10.1038/s41572-021-00247-4. PMID: 33627670; PMCID: PMC8655458.

[6] Boscarino JA, Rukstalis MR, Hoffman SN, Han JJ, Erlich PM, Ross S, Gerhard GS, Stewart WF. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. J Addict Dis. 2011 Jul-Sep;30(3):185-94. doi: 10.1080/10550887.2011.581961. PMID: 21745041.

[7] Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *Journal of Clinical Epidemiology*. 2020;119:126-135. doi:10.1016/j.jclinepi.2019.10.014)

Comment #2: Data analysis: How the authors converted continuous measures to some scales (e.g., VAS, SF-36, etc.). Why did you choose this method over z-scores or other comparable techniques?

Answer to comment #2: To clarify how we converted the continuous measures, we added the following underlined text in the data analysis section:

- *"We converted continuous measures to common scales on a domain-by-domain basis when different instruments were used to measure the same construct by re-scaling the mean and SD of the other instruments."*

Details on converting continuous measures can also be found in Thorland et al. which we reference in our manuscript (reference 25).

Regarding the second question, we did not pool continuous outcomes using z score or standardized mean difference because these methods are inferior and not recommended for several reasons highlighted in these references.[8,9] It has also been shown[10] that clinician are more likely to understand pooled continuous outcomes when reported as the risk difference of achieving the minimally important difference versus z-scores.

For these reasons, we did not analyze the pool continuous outcomes using z score and/or standardized mean difference.

Comment #3: It would be interesting to add one more subgroup analysis: CBD vs. THC vs. mixed CBD/THC (or others).

[8] Johnston BC, Patrick DL, Thorlund K, Busse JW, da Costa BR, Schünemann HJ, Guyatt GH. Patient-reported outcomes in meta-analyses-part 2: methods for improving interpretability for decision-makers. Health Qual Life Outcomes. 2013 Dec 21;11:211. doi: 10.1186/1477-7525-11-211. PMID: 24359184; PMCID: PMC3984637.

[9] Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. Res Synth Methods. 2011 Sep;2(3):188-203. doi: 10.1002/jrsm.46. Epub 2011 Dec 14. PMID: 26061786.

[10] Johnston BC et al. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. CMAJ. 2016 Jan 5;188(1):25-32. doi: 10.1503/cmaj.150430. Epub 2015 Oct 26. PMID: 26504102; PMCID: PMC4695351.)

Answer to comment #3: In a medical cannabis systematic review and meta-analysis study by Wang et al 2021[11], the authors performed subgroup effects by cannabis type. They did not find any credible subgroup effect, which may be explained by the fact that these analyses were underpowered. Our study faces a similar limitation due to the limited number of trials which could inform sub-group analyses by cannabis types. As shown in Table 1, two trials involved PEA; 11 involved THC/CBD; 7 involved THC; 2 involved CBD; and 1 trial involved CBDV).

For these reasons, we did not conduct subgroup analyses by cannabis type.

Comment #4: Please add more comments about transitivity and publication bias to the discussion.

Answer to comment #4: To address the reviewer's comment, we have added text in the methods and discussion which are described below.

The following underlined text has been added in the methods section:

- *"The feasibility of conducting a random effects Bayesian NMA was assessed for all outcomes – this included assessing homogeneity of included studies, patients, and intervention characteristics, and network connectivity."*

We also updated the discussion with the following underlined text:

- *"We do not feel our analysis suffers from serious intransitivity as the distribution of potential effect modifiers were well balanced across the included studies.[153]*

Regarding publication bias, there is no widely acceptable method to assess small-study effects or other publication-related biases for network meta-analysis. As noted in our methods, we assessed small-study effects using funnel plots and Egger's test when 10 or more trials were available for all direct comparisons (eFigure 18 – eFigure 27).

We address potential small-study effects with the following additional underlined text in our discussion section:

- *"Our results for opioids may be overestimated due to small study effects from the included RCTs for pain relief, physical functioning and sleep and for pain relief in the cannabis for medical use RCTs."*

[11] Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ*. 2021;374:n1034. doi:10.1136/bmj.n1034

Reviewer: 3 Dr. C Feng, University of Rochester

Comments to the Author: The authors did a very comprehensive meta analysis to compare the benefits and harms of opioids and medical cannabis for chronic non-cancer pain. The selection of published clinical trials and statistical analysis support the conclusion.

Comment #1: My only concern is that the paper may be too long for a single issue of the journal.

Answer to comment #1: We are mindful of the length of the document and believe we found a balance between restricting our word count and addressing recommendations from the reviewers and Editor in the main text of the manuscript and the supporting material e.g. e-tables).

Reviewer: 4 Dr. D Moore, Rutgers University

Comments to the Author: This is a large and thorough meta-analysis of cannabis versus opioids for chronic noncancer pain. The search process for studies to include was thorough and appropriate. The findings will be of great value to clinicians dealing with chronic pain. I have two concerns, mainly about the statistical methods:

Comment #1: Network meta-analysis is an important tool, and the authors refer to the Hutton et al. PRISMA extension statement for network meta-analyses. Still, it would help readers to expand on the value of network analysis for this study, possibly including a graph of the network to summarize the numbers of studies and different treatments, such as Figure 1 in the Hutton et al. reference.

Answer to comment #1: We added a new figure (Figure 2) in our manuscript showing the evidence network for all outcomes.

Comment #2: The authors include several funnel plots in the appendix which to this reader appear to show some publication bias. Please comment on these funnel plots and explain how this may or may not affect their conclusions.

Answer to comment #2: As per our answer to comment #4 of Reviewer 2, regarding publication bias, there is no widely acceptable method to assess small-study effects or other publication-related biases for network meta-analysis. As noted in our methods, we assessed small-study effects using funnel plots and Egger's test when 10 or more trials were available for all direct comparisons (eFigure 18 – eFigure 27).

We address potential small-study effects with the following additional underlined text in our discussion section:

- *"Our results for opioids may be overestimated due to small study effects from the included RCTs for pain relief, physical functioning and sleep and for pain relief in the cannabis for medical use RCTs."*

Reviewer: 5 Dr. Isabel Allen, UCSF

Comments to the Author: Very comprehensive and well done systematic review and meta-analysis.

Comment #1: It would be great to see a network plot with strength of evidence in the main paper since the tables are sometimes difficult to decipher.

Answer to comment #2: Thank you! We added a new Figure 2 showing the network evidence for all our outcomes.

VERSION 2 – REVIEW

REVIEWER	Thammanard Charernboon Thammasat University
REVIEW RETURNED	03-Sep-2023

GENERAL COMMENTS	Cannabis for medical use versus opioids for chronic noncancer pain: A systematic review and network meta-analysis of randomized clinical trials. The authors conducted a comprehensive network meta-analysis to compare the benefits and harms of cannabis for medical use versus opioids in chronic non-cancer pain. This is a highly significant paper that would greatly benefit the academic community. The authors have made significant improvements in the current manuscript. They have adequately addressed my previous recommendations, and I have no further concerns.

REVIEWER	D Moore Rutgers University, Biostatistics
REVIEW RETURNED	18-Sep-2023

GENERAL COMMENTS	The authors responded appropriately to my comments.